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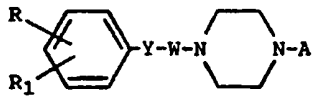

(I)

(57) Abstract

There are disclosed compounds of general formula (I). Y is a linking group, chosen from a wide range, but including -COO-, -CH_2COO-, -CONH-, -CON(CH_3)-, -CH_2CONH-, -SO_2NH-, -SO_2N(CH_3)- and -PO(OC_2H_5)NH-. W is an alkylene chain. A is a substituted phenyl group or a benzofuran or benzodioxan group. R and R_1 may have many values, but R is preferably a bulky group. These compounds and their prodrugs, enantiomers, diastereoisomers, N-oxides and pharmaceutically acceptable salts block α_{1A}-adrenergic receptors and are thus useful for the prevention of contractions of the prostate, urethra and lower urinary tract, without affecting blood pressure.

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TITLE

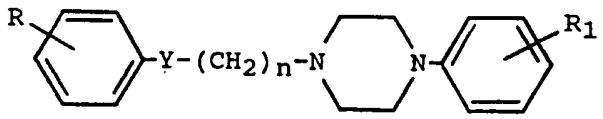
PIPERAZINE DERIVATIVES AS α1A-ADRENERGIC RECEPTOR ANTAGONISTS.

FIELD OF THE INVENTION

The invention relates to piperazine derivatives and to pharmaceutical compositions containing them.

BACKGROUND OF THE INVENTION

Many different derivatives of piperazine are reported in the literature. For example, compounds of the general formula



wherein R = one or more of H, halogen, alkyl and alkoxy,

Y = CO, and

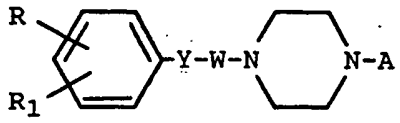
R_1 = H, halogen, methyl or methoxy,

have been reported in US 2997472 as being active on the central nervous system. Other compounds of the same general formula, R_1 and Y having the same meanings but R being a cyclic amino group, are disclosed in ZA 67/05794, and are again said to be active on the central nervous system. Further examples are given in Japanese Kokai 75-108264 where derivatives of this formula (R = H, alkoxy, halogen, Y = NH and R_1 = 2-methoxy) are reported to have antiinflammatory, antipyretic, analgesic and blood pressure depressing activity. The compounds of the invention, described below, essentially include bulky substituents on the phenyl ring linked to Y and/or new values for Y, not yet described in the literature for this class of derivatives. The combination of the above and other structural elements, such as the nature of the piperazine substituent A, gives the new compounds the ability to interact with the α_{1A}-adrenergic receptor, and hence the possibility of selectively relaxing

the tissues where these receptors are present.

SUMMARY OF THE INVENTION

The invention provides compounds of the general formula I:

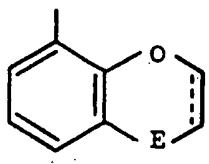


wherein

Y represents a valence bond or one of the following groups, each of which is depicted with its left hand end being the end which attaches to the phenyl group and its right hand end being the end which attaches to the group W:
$-S(O)n-$, $-N(R_2)-$, $-N(R_2)CO-$, $-PO(OC_2H_5)NH-$, $-NHCONH-$, $-CO-$, $-SO_2N(R_2)-$, $-(CH_2)_nCOO-$ and $-(CH_2)_nCON(R_2)-$,
wherein
n is 0 to 2, and
R_2 represents a hydrogen atom, an alkyl group having up to 4 carbon atoms, a carbamoyl group, or an alkanoyl or alkylcarbamoyl group each having from 2 to 5 carbon atoms;

W represents a linear or branched alkylene group having from 2 to 6 carbon atoms;

A represents (i) a substituted phenyl group, the or each substituent being a halogen atom or an alkoxy, alkyl or hydroxy group, the substituent or one of the substituents being in the 2-position, or (ii) a group of the formula



wherein

---- represents a single or double bond, and

E represents an oxygen atom or a valence bond;

R represents a group of the formula $-X-(CH_2)_p-Z$, wherein

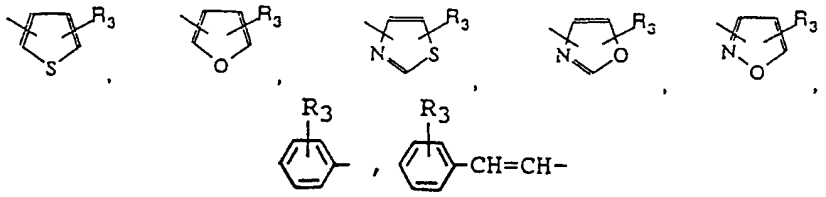
X represents a valence bond or one of the following groups, each of which is depicted with its left hand end being the end which attaches to the phenyl group and its right hand end being the end which attaches to the group $-(CH_2)_p-Z$:

$-O-$, $-S(O)_n-$, $-CO-$, $-N(R_2)-$, $-N(R_2)CO-$ and $-N(R_2)SO_2-$;

wherein n and R_2 are as above defined;

p is 0 to 10, and

Z represents a hydrogen atom, a cycloalkyl group having from 4 to 8 carbon atoms, a 1-naphthyl group, a 2-naphthyl group, a diphenylmethyl group or one of the groups having the following formulae



wherein R_3 has the same values as R_1 defined below; and

R_1 represents one or more hydrogen or halogen atoms or cyano, hydroxy, alkoxy, alkyl, trifluoromethyl, alkanoyl, α-hydroxyalkyl, nitro, amino, alkylamino, dialkylamino, alkanoylamino, alkylsulphonylamino, phenyl, phenoxy or benzoyl groups;

with the provisos that:

when Y represents a valence bond or one of the groups $-S(O)_n-$, $-N(R_2)-$, $-CH_2CON(R_2)-$ or $-CH_2CH_2CON(R_2)-$, Z does not represent a hydrogen atom unless p is greater than 3;

when Y represents one of the groups $-N(R_2)CO-$, $-CO-$ or $-CON(R_2)-$, the group R is in the ortho position

relative to the moiety Y and either (i) the group R_1, not being a hydrogen atom, is in the ortho position relative to the group R or (ii) Z does not represent a hydrogen atom unless p is greater than 3 and

when Y represents a sulphur atom and R represents the group $C_6H_5CH=CHCONH$, R_1 does not represent a hydrogen atom.

The invention further includes prodrugs of the formula I compounds, e.g., the derivatives of compounds of formula I bearing reactive groups such as NH, NH_2 and in particular OH (i.e., at positions R_1 or R_3) prepared for various purposes, e.g., to improve the pharmacokinetic properties (adsorption, distribution, metabolism, plasmatic half-life, etc.) of said compounds of formula I, which can be administered in this "masked" or prodrug form and are liberated, exerting their pharmacological action, in mammals receiving them. Examples of these prodrug derivatives have the following structure:

(Compound of formula I)-OC(O,S)-J-F

wherein

J represents a valence bond, an oxygen or sulphur atom or an amino group,

F represents an alkyl group (optionally containing hetero atoms such as O, S, N or substituted nitrogen), a carbocyclic group or heterocyclic group, optionally substituted with amino, alkylamino, dialkylamino, dialkylaminoalkyl, carboxy, alkoxycarbonyl, carboxamido.

Preferably, J represents a valence bond and F represents a methyl, t-butyl, n-butyl, B-CH_2-phenyl, B-alkyl, B-CO-alkyl, HOCO-alkyl, alkyl-OCO-alkyl, where B represents a dialkylamino group or a cyclic amino group, optionally containing other heteroatoms such as N, O or S. Also included in the invention are derivatives having the formula (Compound I)-OP(O)$(OAlkyl)_2$.

The invention also includes the enantiomers, diastereoisomers, crystalline forms, solvates, N-oxides and

pharmaceutically acceptable salts of these compounds, as well as metabolites of these compounds having the same type of activity (hereafter sometimes referred to as "active metabolites") and prodrugs of said "active metabolites".

The invention further provides pharmaceutical compositions comprising a compound of Formula I or a prodrug, a metabolite, an enantiomer, diastereoisomer, crystalline form, solvate, N-oxide or pharmaceutically acceptable salt of such a compound or prodrug, in admixture with a pharmaceutically acceptable diluent or carrier.

DETAILED DESCRIPTION OF THE INVENTION

The adrenergic antagonistic activity of compounds of the invention renders them useful as agents acting on body tissues particularly rich in α_{1A}-adrenergic receptors (such as blood vessels, prostate, urethra, etc., as reported by A. L. Morrow et al., *Mol. Pharmacol.*, 29, 321, 1986 and references cited therein in general and by M. Suzuki et al., *Jap. J. Pharmacol.*, 58, suppl. 1, 173P, 1992 for the human prostate). As the subclassification of the α_1-receptor subtypes is still in progress and is subject to review and refinement (see e.g. D. A. Schwinn et al., *Eur. J. Pharmacol.-Mol. Pharmacol. Sect.*, 227, 433, 1992), it is intended that the α_{1A} adrenoceptor to which we refer is that one "pharmacologically" characterized (see A. L. Morrow *supra*), which is not alkylated by the selective alkylating agent chloroethylclonidine (CEC), as described in the following experimental pharmacological section.

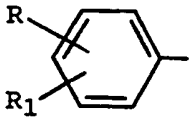
Accordingly, antiadrenergic compounds within the invention established as such on the basis of their receptor binding profile, can be useful therapeutic agents for the treatment, for example, of micturition problems associated with obstructive disorders of the lower urinary tract, including but not limited to benign prostatic hypertrophy (BPH), and of hypertension.

Surprisingly, the compounds of the invention show high selectivity for the mammalian lower urinary tract, i.e., they are substantially more active in antagonizing urethral contractions than in lowering blood pressure. On the contrary, known α_1-antagonists, such as prazosin which is 1-(4-amino-6,7-dimethoxy-2-quinazolinyl)-4-(2-furoyl)-piperazine (GB 1156973), do not exhibit such selectivity (and in fact cause hypotension as a most common side-effect). Urapidil, which is 6-{3-[4-(2-methoxyphenyl)-1-piperazinyl]-propylamino}-1,3--dimethyl-2,4-(1H,3H)-pyrimidinedione, a known antihypertensive drug structurally closer than prazosin to the compounds of this invention, shows a very small selectivity and low affinity for the α_{1A}-adrenoceptor. (Naturally, those compounds of the invention that are not selective for the lower urinary tract are preferred as antihypertensive agents, but even the selective compounds can often be used as antihypertensives because of their low toxicity.)

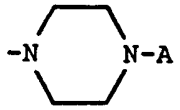
The majority of the compounds of the invention exhibit low toxicity. Thus they can be used in higher amounts, an advantage that often more than compensates for a relatively lower level of activity that some of these compounds have. Naturally, those exhibiting both high activity and low toxicity are preferred.

SYNTHESIS OF THE COMPOUNDS OF THE INVENTION

In this section, the groups



and



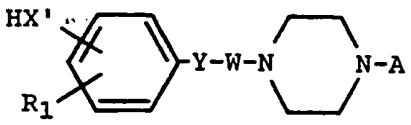
will be abbreviated as RR_1Ph and PzA respectively. L represents a halogen atom or a leaving group such as a tosyloxy group. M represents a group $(CH_2)_n$ wherein n is 0 to 2. Q represents M-CO, SO_2 or $PO(OC_2H_5)$; Q' represents CO

or SO_2. X' represents O, S, N(alkyl) or NH. Hal represents a halogen atom.

The compounds according to the invention may generally be prepared by condensation of compounds $RR_1Ph-Y-W-L$ with compounds H-PzA. The condensation is preferably, but not necessarily, carried out at a temperature of from 20 to 140°C in a polar solvent such as dimethylformamide (DMF) or methanol or in absence of any solvent at 100-200°C, usually in the presence of a base such as potassium carbonate, see Gibson's chapter in Patai, *The Chemistry of the Amino Group*, p.45 et seq., Wiley Interscience, New York, 1968. This alkylation is described in Example 31 below.

Alternatively, under the same conditions, a compound $RR_1Ph-Y-H$ can be condensed with a compound L-W-PzA. This condensation is illustrated in Examples 1 to 5, 9, 10 and 30 below. A particular example of this case is reported in Example 8 below, in which a preformed $RR_1PhCOONa$ is reacted with a compound L-W-PzA in refluxing acetonitrile. When Y=NH, this condensation is preferably carried out on $RR_1Ph-NH-Pg$ derivatives, where Pg is a protecting group which can be easily inserted and cleaved after the condensation has been performed. For example, this may be done by first reacting the amine RR_1Ph-NH_2 with an excess of trifluoroacetic anhydride, then reacting the obtained trifluoroacetyl derivative $RR_1Ph-NH-COCF_3$ with an L-W-PzA reagent and finally deprotecting the resultant trifluoroacetyl derivative of the desired compound of the invention by treatment with potassium carbonate in aqueous methanol or with sodium borohydride in methanol or dimethylsulphoxide (DMSO). Further details on the use of this technique are reported by T.W. Greene in *Protective Groups in Organic Synthesis*, page 353, Wiley Interscience, 1991 and references cited therein.

Another condensation method forms the group R by condensing a compound $Z-(CH_2)_p-L$ with a compound



This condensation can be carried out as above described or by operating in protic or aprotic solvents (e.g. ethanol, acetonitrile, DMF, toluene) in the presence of a base such as potassium carbonate, sodium or sodium hydride at 20-140°C. This condensation is illustrated in Examples 11 to 23, 36, 38, 39 and 42 below.

Some compounds of the invention can be prepared by addition reactions. For example, addition across a double bond is possible, as in:

$$RR_1Ph\text{-}Y\text{-}CH{=}CH_2 + H\text{-}PzA \rightarrow RR_1Ph\text{-}Y\text{-}CH_2CH_2\text{-}PzA$$

(Y=CO or $N(R_2)CO$; R_2=H, C_1-C_4 alkyl), the reaction being carried out in aprotic solvents (e.g., toluene, xylene, DMSO, DMF) at from 25 to 150°C.

Other synthetic schemes include the formation of Y or W during the reaction. Examples are:

$$RR_1Ph\text{-}Q\text{-}Cl + R_2\text{-}NH\text{-}W\text{-}PzA \rightarrow RR_1Ph\text{-}Q\text{-}NR_2\text{-}W\text{-}PzA$$

(R_2=H, C_1-C_4 alkyl). The amidification is carried out in aprotic solvents e.g. haloalkanes, toluene, DMF or pyridine, optionally in the presence of an organic base such as triethylamine, or in aqueous dioxane or lower alkanols in the presence of inorganic bases such as sodium hydroxide, sodium bicarbonate or potassium carbonate, according to Beckwith in Zabicky, *The Chemistry of Amides*, page 731-857, Wiley, 1970. Such a reaction is illustrated in Examples 7, 28, 29, 41 and 43 below.

$$RR_1Ph\text{-}M\text{-}COOH + R_2\text{-}NH\text{-}W\text{-}PzA \rightarrow RR_1Ph\text{-}M\text{-}CONH\text{-}W\text{-}PzA$$

This reaction is carried out in the presence of a coupling agent (e.g. dicyclohexylcarbodiimide, N,N'-carbonyldiimidazole or diethyl cyanophosphonate) optionally in the presence of a promoting agent (e.g. 4-dimethylaminopyridine or N-hydroxybenzotriazole or N-hydroxysuccinimide) in an aprotic or a chlorinated solvent

(e.g. DMF, chloroform) at from -10 to 140°C (Albertson, *Org. React.*, 12, 205-218, 1962; Doherty et al., *J. Med. Chem.*, 35, 9, 1992; Staab et al., *Newer Methods Prep. Org. Chem.*, 5, 61, 1968; Ishihara, *Chem. Pharm. Bull.*, 39, 3236, 1991). It is illustrated in Examples 6, 25 to 27, 32 to 35, 37, 40, 44 and 45 below.

RR_1Ph-M-COOH + alkylchloroformate in the presence of a tertiary amine (e.g. triethylamine) followed by addition of R_2-NH-W-PzA at from 0 to 80°C; optionally a promoting agent (e.g. 1-hydroxypyridine) may be added before the amine addition (Albertson, *Org. React.*, 12, 157, 1962).

RR_1Ph-M-COOH + R_2-NH-W-PzA → RR_1Ph-M-CONH-W-PzA

This reaction can be carried out without a solvent at from 150 to 220°C (Mitchell et al., *J. Am. Chem. Soc.*, 53, 1879, 1931) or in high-boiling ethereal solvents (e.g. diglyme).

RR_1Ph-M-COO-Alk + R_2-NH-W-PzA → RR_1Ph-M-CONH-W-PzA

RR_1Ph-N(R_2)-H + Cl-Q'-W-PzA → RR_1Ph-N(R_2)-Q'-W-PzA

RR_1Ph-N(R_2)-H + HOOC-W-PzA → RR_1Ph-N(R_2)-CO-W-PzA

(R_2=H or C_1-C_4 alkyl). These reactions may be carried out in an aprotic solvent such as hexane or in a chlorinated solvent such as dichloromethane at from -10 to 80°C, or without solvents at from 80 to 180°C. A coupling agent such as trimethylaluminium may be present. See S.M. Weinreb et al., *Tetrahedron*, 4171, 1977; and M.F. Lipton et al., *Org. Synth.*, 59, 49, 1979.

RR_1Ph-M-CO-Hal + HO-W-PzA → RR_1Ph-M-COO-W-PzA

A simple esterification, as shown in Example 24.

RR_1Ph-NH_2 + OHC-W-PzA → RR_1Ph-NH-W-PzA

This reductive amination can be carried out in a lower alkanol as solvent at from 20 to 120°C. Sodium cyanoborohydride is suitable as the reducing agent.

RR_1Ph-Y-Alk-CHO + H-PzA → RR_1Ph-Y-W-PzA

In the conditions described for the previous reaction. This method is not suitable when Y=CO, COO or CH_2COO.

RR_1Ph-$COCH_3$ + CH_2O + H-PzA → $RR_1PhCOCH_2CH_2PzA$

This reaction can be carried out using formaldehyde or a polymer thereof in the presence of a mineral acid in alcohols, acetic acid or acetic anhydride at reflux, as

reported by Tramontini et al. in *Tetrahedron*, 46, 1791, 1990 and references cited therein.

Some of the compounds of the invention may be prepared by conversion of other compounds of the invention. For example:

- Compounds I in which R_1 or R_3 represents an amino group may be prepared by reduction of the corresponding compounds in which R_1 or R_3 represents a nitro group. The reduction can be effected:
  (a) with Ni-Raney catalyst in a protic solvent selected from methanol, ethanol, isopropanol, water and mixtures of them; or
  (b) with $SnCl_2$, H_2O, optionally in presence of hydrochloric acid, either in a protic solvent such as methanol, ethanol, isopropanol, water, acetic acid or a mixture thereof, or in an aprotic solvent such as ethyl acetate; or
  (c) with Fe and aqueous hydrochloric acid in a protic solvent such as methanol, ethanol, isopropanol, water or a mixture thereof.

  The temperatures of the above reactions will be from 20°C to 100°C (J. March, *Advanced Organic Chemistry*, III Ed., page 1103, Wiley Interscience, 1985).
- Compounds I in which R_1 or R_3 represents an amino group may be treated with an alkylating agent L-alkyl to give the corresponding compounds in which R_1 or R_3 represents an alkylamino or dialkylamino group. For monoalkylation, the amino group may be protected before the alkylation and deprotected afterwards, as above described. An alternative alkylation method comprises reacting such compounds with an appropriate aldehyde in the presence of a reducing agent, such as sodium cyanoborohydride, in a lower alkanol as solvent at from 20 to 100°C.
- Compounds I in which R_1 or R_3 represents an alkanoylamino or alkylsulphonylamino group may be prepared by reaction of the corresponding compounds in which R_1 or R_3 represents an amino group with an appropriate alkanoyl or alkylsulphonyl halide or anhydride, in a non-protic

solvent, such as chloroform, 1,2-dichloroethane, toluene, acetone or pyridine in the optional presence of a base such as potassium carbonate or triethylamine at from 20 to 120°C.

- Compounds I in which R_1 or R_3 represents a hydroxy group may be prepared by desalkylation of the corresponding compounds in which R_1 or R_3 represents an alkoxy group. This can be accomplished by treatment with BBr_3 in dichloromethane at from 0 to 40°C (T.W. Greene, *Protective Groups in Organic Synthesis*, page 87, Wiley Interscience, 1981) or according to other methods described in the same reference.
- Compounds I in which R_1 represents an α-hydroxyalkyl group may be prepared by reduction of the corresponding compounds in which R_1 represents an alkanoyl group. Such reduction may be effected with sodium borohydride or sodium cyanoborohydride in a lower alkanol as solvent at from 0 to 90°C.
- Compounds I in which Y represents a group -NH- may be converted to corresponding compounds in which Y represents a group $-N(R_2)-$, R_2 being other than a hydrogen atom. In particular, alkylation can be effected with an alkylating agent L-alkyl or with an aldehyde in reductive conditions, both methods being as described above. Acylation can be effected with an alkanoyl halide or anhydride as described above. Carbamoylation can be achieved by reacting the compound in which Y represents a group -NH- with an inorganic cyanate salt, e.g. potassium cyanate, in acetic acid at from 20 to 100°C. Likewise, in the same conditions or in non-protic solvents such as toluene, chloroform or DMF, the compounds in which R_2=alkylcarbamoyl can be formed using alkyl isocyanates.
- Compounds of formula I having Y=NH can be prepared by reduction of the corresponding compounds I in which Y=NHCO and W has one less carbon atom, the reduction suitably being performed with lithium aluminium hydride or other hydrides, such as borane, or mixed hydrides, operating in aprotic solvents (e.g., diethyl ether, tetrahydrofuran) at

from 20 to 60°C, as described by J. March in *Advanced Organic Chemistry*, IV Ed, page 1219, Wiley Interscience, 1992.

N-oxides of the compounds of the invention may be formed by oxidising the basic nitrogen atom(s) present, mainly, but not necessarily only, that at position 1 of the piperazine ring. The oxidation can be performed by reacting compounds of formula I with hydrogen peroxide at from 20 to 60°C in acetic acid or with m-chloroperbenzoic acid or magnesium mono-peroxyphthalate at from 0 to 50°C, according to Broughan et al., *Synthesis*, 11, 1015, 1987.

Persons skilled in the art will be aware that all the above synthetic pathways might be simplified provided that the reacting intermediates do not bear further groups sensitive to the same reactants (for example : CO, NH_2, NHAlk or OH groups). Compounds of formula I bearing such reactive groups can be prepared through the above paths provided that the reactive groups present in the starting materials are protected beforehand and then deprotected after the reaction. Several examples of protection and deprotection for various reactive groups can be found in T.W. Greene, *Protective Groups in Organic Synthesis*, Wiley Interscience, 1991. Alternatively, unreactive groups (e.g. NO_2) can be left unconverted during the first reaction and then converted to reactive ones (e.g. NH_2) as a final step of the pathway.

Which synthetic technique will be preferred depends on the compound desired to be synthesized. Additional synthetic methods will be apparent to those skilled in the art.

Prodrugs as above defined may be prepared from the corresponding hydroxy compounds of the invention by the following methods:

- by reaction with a chloroformate, an isocyanate or isothiocyanate, a carbonyl chloride or bromide or another

activated acid derivative (e.g. an anhydride) in a suitable solvent (e.g. a chlorinated solvent, DMF, tetrahydrofuran, dioxane, acetonitrile, pyridine) in the presence or otherwise of a base such as triethylamine, pyridine, 4-dimethylaminopyridine, sodium hydroxide, potassium carbonate or 1,10-diazabicycloundecene at from -20 to 100°C;

- by reaction with a carboxylic acid in one of the solvents above specified, in the presence of a condensing agent such as N,N'-carbonyldiimidazole or a carbodiimide;
- by reaction with a dialkyl or diaryl chlorophosphate or dialkyl cyanophosphonate in the same conditions described above (for examples of such derivatization methods see S.O. Thorberg et al., *J. Med. Chem.*, 30, 2008, 1987).

DETAILED PREPARATION OF INTERMEDIATES

Ethyl 2-benzyloxy-3-propionylbenzoate
Intermediate I

A mixture of 11.1 g of ethyl 2-hydroxy-3-propionylbenzoate, prepared as described in DE 2059296, 27.64 g of anhydrous potassium carbonate and 8.58 g of benzyl bromide in 250 ml of ethyl acetate was stirred at reflux for 4 hours. After cooling the reaction mixture to room temperature, insoluble matter was removed by suction filtration and the filtrate was evaporated to dryness yielding quantitatively the title compound, used without further purification (GLC assay was 99%). B.p. 195-205°C (2 mmHg).

2-Benzyloxy-3-propionylbenzoic acid
Intermediate II

A mixture of 4.68 g of Intermediate I and 90 ml of 2N sodium hydroxide in 38 ml of ethanol was stirred at 80°C for 2 hours. After this period, the organic solvent was removed by evaporation in vacuo. The residue was rinsed with 90 ml of water and extracted with diethyl ether; the aqueous layer

was acidified (pH=1) by adding 37% HCl and extracted with ethyl acetate. The organic layer was washed with water to neutrality, dried on sodium sulphate and evaporated to dryness in vacuo yielding the title compound, used without further purification. It melted at 65-67°C after repeated crystallization from petroleum ether:diethyl ether 8:2.

2,2-Dimethyl-3-[4-(2-methoxyphenyl)-1-piperazinyl]--propionaldeyde dihydrochloride
Intermediate III

A mixture of 3 g of 1-(2-methoxyphenyl)-piperazine dihydrochloride, 0.4 g of paraformaldehyde and 1 ml of isobutyraldehyde in 4 ml of ethanol was stirred at reflux for 1.5 hours. 0.4 g of paraformaldehyde was added and the mixture was stirred again for 1½ hours at reflux. After cooling to room temperature, water was added and the resulting solution was washed twice with diethyl ether, made alkaline by adding 1N aqueous sodium hydroxide solution and extracted with diethyl ether. The organic layer was washed with water, dried on sodium sulphate and evaporated to dryness in vacuo. The crude product was purified by flash chromatography on silica gel eluting with ethyl acetate. Evaporation in vacuo of the collected fractions yielded 2.1 g of the base of the title compound. This was dissolved in diethyl ether and acidified with 3.8N hydrochloric acid in diethyl ether. The title compound was recovered by suction filtration and melted at 181-183°C.

1-(2,2-Dimethyl-3-hydroxypropyl)-4-(2-methoxyphenyl)--piperazine dihydrochloride
Intermediate IV

1.44 g of sodium borohydride was added portionwise at 0°C to a solution of 11.64 g of the base of Intermediate III in 90 ml of ethanol. The reaction mixture was stirred at room temperature for 24 hours. It was then cooled to 0°C, acidified to pH = 1 with 3N hydrochloric acid and extracted

with ethyl acetate. The organic layer was washed with water, dried on sodium sulphate and evaporated to dryness in vacuo. The oily residue was purified by flash chromatography eluting with petroleum ether:ethyl acetate 6:4. Evaporation in vacuo of the collected fractions yielded 7.29 g of the base of the title compound, and this was converted in the usual manner into its hydrochloride salt. It melted at 203-205°C after crystallization from ethyl acetate, followed by acetonitrile.

Benzyl 3-acetyl-2-benzyloxybenzoate
Intermediate V

A mixture of 3.5 g of 3-acetyl-2-hydroxybenzoic acid (prepared as described by R.E. Ford., *J. Med. Chem.*, 29, 538, 1986), 5.3 ml of benzyl bromide and 4.17 g of anhydrous potassium carbonate in 40 ml of anhydrous DMF was stirred at 80°C for 4 hours. After cooling to room temperature, the reaction mixture was poured into water and extracted with diethyl ether. The organic layer was dried on sodium sulphate, evaporated to dryness in vacuo and purified by flash chromatography, eluting with a petroleum ether:ethyl acetate 9:1 mixture. Yield: 6.05 g of the pure title compound. M.p. 42-47°C (n-hexane:cyclohexane 1:1).

3-Acetyl-2-benzyloxybenzoic acid
Intermediate VI

A mixture of 5.46 g of Intermediate V and 30 ml of 1N sodium hydroxide in 75 ml of 95% ethanol was stirred for 7 hours at room temperature. The solvent was evaporated off in vacuo and the residue was diluted with water and acidified (pH=1) with 1N hydrochloric acid. Extraction with ethyl acetate followed by the usual procedure yielded 5.32 g of the pure title compound.

^{1}H-NMR spectrum at 60 MHz, $CDCl_3$ (δ)

10.6 (bs, 1H, COOH)

8.25 (dd, 1H, CH in position 6 of the benzoic acid)

7.90	(dd, 1H, CH in position 4 of the benzoic acid)
7.20-7.70	(m, 6H, CH in position 5 of the benzoic acid and benzyl CHs)
5.10	(s, 2H, CH_2)
2.60	(s, 3H, CH_3)

2-(4-Nitrobenzyloxy)-3-propionylbenzoic acid
Intermediate VII

A mixture of 2.2 g of ethyl 2-hydroxy-3-propionylbenzoate, 3.24 g of 4-nitrobenzyl chloride and 2.07 g of anhydrous potassium carbonate in 20 ml of anhydrous DMF was stirred at 80°C for 3 hours. After cooling to room temperature, the reaction mixture was poured into water and extracted with ethyl acetate. After the usual work-up, the crude was purified by flash chromatography eluting with a petroleum ether:ethyl acetate 8:2 mixture. Evaporation in vacuo of the solvents from the pooled fractions gave 2.84 g of pure ethyl 2-(4-nitrobenzyloxy) -3-propionylbenzoate, characterized by NMR spectroscopy, as follows.

^{1}H-NMR spectrum at 60 MHz, $CDCl_3$ (δ)

8.10-8.35	(m, 2H, CHs at positions 3, 5 of the nitrophenyl)
8.00	(dd. 1H, CH at position 6 of the benzoate)
7.50-7.80	(m, 3H, CHs at position 4 of the benzoate and at positions 2, 6 of the nitrophenyl)
7.3	(dd, 1H, CH at position 5 of the benzoate)
5.10	(s, 2H, CH_2Ph)
4.35	(q, 2H, CH_2O)
2.90	(q, 2H, CH_2CO)
1.15-1.35	(2xt, 6H, 2 x CH_3)

2.42 g of the so obtained ester was hydrolyzed following the procedure described for Intermediate VI. Yield: 2.02 g of the title compound. M.p. 103-107°C (toluene:petroleum ether 1:1).

Ethyl 2-(4-benzoylbenzyloxy)-3-propionylbenzoate

Intermediate VIII

A solution of 11.89 g of 4-methylbenzophenone, 12.82 g of N-bromosuccinimide and 0.3 g of benzoylperoxide in 30 ml of tetrachloromethane was refluxed for 6½ hours. Filtration of the precipitated succinimide followed by evaporation to dryness of the mother liquor yielded 17.2 g of crude 4-benzoylbenzyl bromide (73% by NMR) used without further purification.

The title compound was synthesized according to the first step of the method described for the preparation of Intermediate VII, but starting from 2.64 g of ethyl 2-hydroxy-3-propionylbenzoate and using 4.96 g of the 73% 4-benzoylbenzyl bromide instead of 4-nitrobenzyl chloride. Purification by flash chromatography (eluent: petroleum ether:ethyl acetate 8:1) yielded 4.1 g of the pure title compound as an oil.

Elemental Analysis for $C_{26}H_{24}O_5$:
Calc.: C, 74.98; H, 5.81.
Found: C, 75.11; H, 5.82.

2-(4-Benzoylbenzyloxy)-3-propionylbenzoic acid.
Intermediate IX

The title compound was prepared according to the procedure described for Intermediate VI but starting from Intermediate VIII instead of Intermediate V. M.p. 139-141°C (toluene).

2-Benzyloxy-N-(3-hydroxypropyl)-benzamide
Intermediate X

A solution of 22.83 g of 2-benzyloxybenzoic acid (prepared as described in *J. Am. Chem. Soc.*, 65, 2140, 1943), 15.9 ml of thionyl chloride and 130 ml of ethanol-free chloroform was stirred at reflux temperature for 3½ hours. After cooling to room temperature, the mixture was evaporated to

dryness in vacuo to give 23.94 g of crude 2-benzyloxybenzoyl chloride, used without purification. A solution of the above intermediate in 100 ml of dichloromethane was added dropwise at room temperature to a stirred solution of 8.4 g of 3-aminopropanol, 15.5 ml triethylamine and 100 ml of dichloromethane. The mixture was stirred at 20-25°C for 2 hours, and then successively washed with 2N hydrochloric acid, water, 5% aqueous sodium bicarbonate, and water. The organic layer was dried over anhydrous sodium sulphate and evaporated to dryness in vacuo to give 26.6 g of the title compound. M.p. 117-119°C after crystallization from isopropyl acetate.

2-Benzyloxy-N-(3-chloropropyl)-benzamide
Intermediate XI

A solution of 4.4 ml of thionyl chloride in 45 ml of ethanol-free chloroform was added dropwise within 20 minutes to a refluxing solution of 8.64 g of Intermediate X in 120 ml of ethanol-free chloroform. The mixture was stirred at reflux temperature for 3 hours and then cooled to room temperature. It was washed successively with water, 5% aqueous sodium bicarbonate, and water. The organic layer was dried over anhydrous sodium sulphate and evaporated to dryness in vacuo to give 10.3 g of the title compound whose structure was confirmed by NMR spectroscopy, as follows.

NMR spectrum at 200 MHz, $CDCl_3$ (δ)

8.22	(dd, 1H, CH in position 6 of benzamide ring)
7.90-8.05	(bs, 1H, CONH)
7.38-7.46	(m, 6H, CH in position 4 of benzamide ring and aromatic CHs of benzyl ring)
7.02-7.10	(m, 2H, CHs in positions 3 and 5 of benzamide ring)
5.15	(s, 2H, OCH_2)
3.47	(q, 2H, $NHC\underline{H}_2CH_2CH_2Cl$)
3.36	(t, 2H, $NHCH_2CH_2C\underline{H}_2Cl$)
1.86	(m, 2H, $NHCH_2C\underline{H}_2CH_2Cl$)

DETAILED PREPARATION OF THE COMPOUNDS OF THE INVENTION

Example 1

3-[4-(2-Methoxyphenyl)-1-piperazinyl]-propyl benzoate dihydrochloride

A mixture of 1.8 g of benzoic acid and 2.08 g of anhydrous potassium carbonate in 40 ml of anhydrous DMF was stirred at 80°C for 1 hour. The reaction mixture then was cooled to room temperature, and 3.5 g of 1-(3-chloropropyl)--4-(2-methoxyphenyl)-piperazine was added. The mixture was stirred at 50°C for 3 hours and then once again cooled to room temperature. It was poured into water and filtered under suction to give the crude base of the title compound. This crude base was dissolved in 50 ml of ethanol and 9 ml of 5N ethanolic hydrogen chloride was added. The crystals which precipitated were recovered by suction, yielding 4.5 g of the title compound (m.p. 219-220°C).

Example 2

3-[4-(2-Methoxyphenyl)-1-piperazinyl]-propyl 2-methoxybenzoate dihydrochloride . 0.25-H_2O

The title compound was prepared following the procedure described in Example 1, but using 2-methoxybenzoic acid instead of benzoic acid and extracting with dichloromethane instead of filtering. M.p. 205-206°C (ethanol).

Example 3

3-[4-(2-Methoxyphenyl)-1-piperazinyl]-propyl 2-benzyloxybenzoate dihydrochloride

The title compound was prepared following the method described in Example 1 but using 2-benzyloxybenzoic acid

(prepared as described in *J. Am. Chem. Soc.*, 65, 2140, 1943) instead of benzoic acid and extracting with dichloromethane instead of filtering. M.p. 201-203°C (ethanol).

Example 4

3-[4-(2-Methoxyphenyl)-1-piperazinyl]-propyl 2-methoxy-3-propionylbenzoate dihydrochloride

The title compound was obtained following the procedure of Example 1 but starting from 2-methoxy-3-propionylbenzoic acid, (prepared as described in JP 6064944) instead of benzoic acid, and extracting with ethyl acetate instead of filtering. M.p. 192-193°C (ethanol).

Example 5

3-[4-(2-Methoxyphenyl)-1-piperazinyl]-propyl 2-benzyloxy-3-propionylbenzoate dihydrochloride

The title compound was obtained following the procedure described in Example 1 but using Intermediate II instead of benzoic acid. The reaction mixture was extracted with dichloromethane instead of filtering. After conversion into its dihydrochloride, the title compound melted at 175-176°C (ethanol).

Example 6

2-Benzyloxy-N-{3-[4-(2-methoxyphenyl)-1-piperazinyl]--propyl}-benzamide dihydrochloride . 0.25-H_2O

0.94 g of 1,1'-carbonyldiimidazole was added portionwise at 0°C to a stirred solution of 2.56 g of 2-benzyloxybenzoic acid in 25 ml of anhydrous tetrahydrofuran. Stirring was continued for 1 hour at the same temperature; afterwards 3.35 g of 1-(3-aminopropyl)-4-(2-methoxyphenyl)-piperazine (prepared as described in GB 2161807) was added and the

reaction mixture was stirred at room temperature for a further 1½ hours. The solvent was removed by evaporation in vacuo and the residue was rinsed with water and extracted with ethyl acetate. The organic layer was washed with water, dried on anhydrous sodium sulphate and evaporated to dryness in vacuo. The crude product was purified by flash chromatography on silica gel eluting with ethyl acetate, yielding 4.63 g of the title compound as a base, which was converted in the usual manner into its dihydrochloride, m.p. 179-180°C (ethanol).

Example 7

2-Hydroxy-N-{3-[4-(2-methoxyphenyl)-1-piperazinyl]-propyl}--3-propionylbenzamide dihydrochloride

A solution of 7.48 g of 1-(3-aminopropyl)--4-(2-methoxyphenyl)-piperazine in 30 ml of dichloromethane was added dropwise over a period of 45 minutes at 4°C into a stirred mixture of 6.37 g of 2-hydroxy-3-propionylbenzoyl chloride (prepared as described in DE 2631248) and 4.2 ml of triethylamine in 80 ml of dichloromethane. The reaction mixture was stirred for 2 hours at 4°C and for 8 hours at room temperature, and was then extracted with 5% aqueous sodium hydrogen carbonate solution followed by water. The organic layer was dried over anhydrous sodium sulphate. The residue obtained by evaporation in vacuo of the solvent was purified by flash chromatography on silica gel eluting with dichloromethane:methanol graduated 98:2 to 95:5. The fractions containing the pure base were pooled, the solvents were evaporated off in vacuo, the residue was dissolved in ethanol and an excess of ethanolic hydrogen chloride was added. Diethyl ether was added until crystallization of the salt. 7.6 g of the title compound was obtained after recrystallization from methanol. M.p. 215-217°C with decomposition.

Example 8

3-[4-(2-Methoxyphenyl)-1-piperazinyl]-propyl 2-hydroxybenzoate monomethanesulphonate

A mixture of 17.6 g of sodium salicylate, 26.9 g of 1-(3-chloropropyl)-4-(2-methoxyphenyl)-piperazine and 35 ml of acetonitrile was stirred at reflux temperature for 5 hours. After cooling to room temperature, the reaction mixture was poured into 500 ml of water and extracted with dichloromethane. The organic layer was separated, dried over anhydrous sodium sulphate and evaporated in vacuo giving 32.1 g of the title compound as a base. This was converted into its monomethanesulphonate by the usual method. M.p. 156-157°C (ethanol:diethyl ether).

Example 9

3-[4-(2-Methoxyphenyl)-1-piperazinyl]-propyl 3-benzyloxybenzoate dihydrochloride

A mixture of 0.91 g of 3-benzyloxybenzoic acid (prepared as described in *J. Chem. Soc.*, 430, 1943), 1.7 g of anhydrous potassium carbonate and 35 ml of anhydrous DMF was stirred for 30 minutes at 80°C. After cooling to room temperature, 1.37 g of 1-(3-chloropropyl)-4-(2-methoxyphenyl)-piperazine dihydrochloride was added to the reaction mixture, which was then stirred for 3 hours at 80°C. After quenching with 500 ml of water, the precipitate was extracted with diethyl ether. The organic layer was washed first with 5% aqueous sodium hydrogen carbonate solution and then with water, dried over anhydrous sodium sulphate and evaporated to dryness. The residue was dissolved in ethanol and an excess of ethanolic hydrogen chloride was added to the solution, yielding 1.4 g of the title compound, after recrystallization from ethanol. M.p. 194-195°C.

Example 10

3-[4-(2-Methoxyphenyl)-1-piperazinyl]-propyl 4-benzyloxybenzoate dihydrochloride . 0.75-H_2O.

The title compound was prepared according to Example 9 but using 4-benzyloxybenzoic acid (prepared as described in *J. Am. Chem. Soc.*, 65, 2140, 1943) instead of 3-benzyloxybenzoic acid. M.p. 200-202°C (ethanol).

Example 11

3-[4-(2-Methoxyphenyl)-1-piperazinyl]-propyl 2-(2-chlorobenzyloxy)-benzoate monomethanesulphonate

A mixture of 3.5 g of the product prepared in Example 8, 6.9 g of anhydrous potassium carbonate and 5 ml of acetonitrile was stirred at reflux temperature. After 15 minutes, a solution of 1.72 g of 2-chlorobenzyl chloride in 5 ml of acetonitrile was added dropwise and heating was continued for further 4 hours.
After cooling to room temperature, the reaction mixture was diluted with 10 ml of water and extracted with 20 ml of dichloromethane. The organic layer was separated, dried over anhydrous magnesium sulphate, and evaporated to dryness in vacuo. The crude base was purified by flash chromatography on silica gel eluting with acetone:petroleum ether 1:3. The pure base was dissolved in ethanol and one equivalent of a 2N ethanolic solution of methanesulphonic acid was added, followed by diethyl ether addition until crystallization of the salt. 3.4 g of the title compound was obtained after recrystallization from ethanol:diethyl ether (m.p. 114-117°C).

Example 12

3-[4-(2-Methoxyphenyl)-1-piperazinyl]-propyl 2-(3-chlorobenzyloxy)-benzoate monomethanesulphonate

This compound was prepared according to the method described in Example 11 but using 3-chlorobenzyl chloride instead of 2-chlorobenzyl chloride and the reaction lasted 20 hours. The title compound was crystallized from ethanol:diethyl ether and melted at 140-143°C.

Example 13

3-[4-(2-Methoxyphenyl)-1-piperazinyl]-propyl 2-(4-chlorobenzyloxy)-benzoate monomethanesulphonate hemihydrate

This compound was prepared according to the method described in Example 11 but using 4-chlorobenzyl chloride instead of 2-chlorobenzyl chloride and the reaction lasted 16 hours. The title compound was crystallized from ethanol:diethyl ether and melted at 143-146°C.

Example 14

3-[4-(2-Methoxyphenyl)-1-piperazinyl]-propyl 2-(2-methoxybenzyloxy)-benzoate monomethanesulphonate

This compound was prepared according to Example 11 but using 2-methoxybenzyl chloride instead of 2-chlorobenzyl chloride and the reaction lasted 5 hours. The title compound was crystallized from ethanol:diethyl ether and melted at 117-119°C.

Example 15

3-[4-(2-Methoxyphenyl)-1-piperazinyl]-propyl 2-(3-methoxybenzyloxy)-benzoate monomethanesulphonate

This compound was prepared according to Example 11 but using 3-methoxybenzyl chloride instead of 2-chlorobenzyl chloride. The title compound was crystallized from ethanol:diethyl ether and melted at 125-126.5°C.

Example 16

3-[4-(2-Methoxyphenyl)-1-piperazinyl]-propyl 2-(4-methoxybenzyloxy)-benzoate monomethanesulphonate hydrate

This compound was prepared according to Example 11 but using 4-methoxybenzyl chloride instead of 2-chlorobenzyl chloride and the reaction lasted 7 hours. The title compound was crystallized from ethanol:diethyl ether and melted at 128-132°C.

Example 17

3-[4-(2-Methoxyphenyl)-1-piperazinyl]-propyl 2-(2,3-dimethoxybenzyloxy)-benzoate monomethanesulphonate

This compound was prepared according to Example 11 but using 2,3-dimethoxybenzyl chloride instead of 2-chlorobenzyl chloride and the reaction lasted 2 hours. The title compound was crystallized from ethanol:diethyl ether and melted at 141-143°C.

Example 18

3-[4-(2-Methoxyphenyl)-1-piperazinyl]-propyl 2-(3,4-dimethoxybenzyloxy)-benzoate monomethanesulphonate

This compound was prepared according to Example 11 but using 3,4-dimethoxybenzyl chloride instead of 2-chlorobenzyl chloride and the reaction lasted 2 hours. The title compound was crystallized from ethanol:diethyl ether and melted at 132-135°C.

Example 19

3-[4-(2-Methoxyphenyl)-1-piperazinyl]-propyl 2-(3,4,5--trimethoxy-benzyloxy)-benzoate monomethanesulphonate 0.75-H_2O

This compound was prepared according to Example 11 but using 3,4,5-trimethoxybenzyl chloride instead of 2-chlorobenzyl chloride and the reaction lasted 2 hours. The title compound was crystallized from ethanol:diethyl ether and melted at 97-103°C.

Example 20

3-[4-(2-Methoxyphenyl)-1-piperazinyl]-propyl 2-octyloxybenzoate monomethanesulphonate hydrate.

This compound was prepared according to Example 11 but using 1-bromooctane instead of 2-chlorobenzyl chloride and the reaction lasted 15 hours. The title compound was crystallized from ethanol:diethyl ether and melted at 75-77°C.

Example 21

3-[4-(2-Methoxyphenyl)-1-piperazinyl]-propyl 2-butoxybenzoate monomethanesulphonate hydrate

This compound was prepared according to Example 11 but using 1-bromobutane instead of 2-chlorobenzyl chloride and the reaction lasted 11 hours. The title compound was crystallized from ethanol:diethyl ether and melted at

69-72°C.

Example 22

3-[4-(2-Methoxyphenyl)-1-piperazinyl]-propyl 2-cyclohexylmethoxybenzoate monomethanesulphonate hemihydrate

This compound was prepared according to Example 11 but using cyclohexylmethyl bromide instead of 2-chlorobenzyl chloride and the reaction lasted 33 hours. The title compound was crystallized from ethanol:diethyl ether and melted at 104-106°C.

Example 23

3-[4-(2-Methoxyphenyl)-1-piperazinyl]-propyl 2-(2-naphthylmethoxy)-benzoate monomethanesulphonate hydrate

This compound was prepared according to Example 11 but using 2-bromomethylnaphthalene instead of 2-chlorobenzyl chloride and the reaction lasted 30 hours. The title compound was crystallized from ethanol:diethyl ether and melted at 101-103°C.

Example 24

2,2-Dimethyl-3-[4-(2-methoxyphenyl)-1-piperazinyl]-propyl 2-benzyloxybenzoate dihydrochloride

A mixture of 2.73 g of 2-benzyloxybenzoic acid, 0.97 ml of thionyl chloride and 0.10 ml of anhydrous DMF in 24 ml of anhydrous dichloromethane was stirred at room temperature for 2½ hours under a nitrogen stream. After this period, the reaction mixture was cooled to 0°C and a solution of 3.67 g of Intermediate IV in 24 ml of anhydrous dichloromethane was added dropwise in 5 minutes. Stirring was continued for 22 hours at room temperature. 40 ml of a 0.4M aqueous solution

of sodium carbonate was then added, followed by 20 ml of dichloromethane. The organic layer was separated off, washed with water, dried on sodium sulphate and evaporated to dryness in vacuo. The oily residue was purified by flash chromatography on silica gel eluting with dichloromethane:ethyl acetate graduated from 100:3 to 100:7.5. Evaporation in vacuo of the collected fractions yielded 4.31 g of the base of the title compound. The base was dissolved in isopropanol and excess isopropanolic hydrogen chloride was added. Crystals were recovered by suction filtration yielding 3.82 g of the title compound, which melted at 188-190°C after recrystallization from acetonitrile.

Example 25

N-{3-[4-(2-methoxyphenyl)-1-piperazinyl]-propyl}-
-2-phenylthio-benzamide dihydrochloride

0.34 ml of diethyl cyanophosphonate was added dropwise at 0-5°C to a stirred solution of 0.46 g of 2-phenylthio-benzoic acid (prepared as described in *J. Am. Chem. Soc.*, 84, 1561, 1962) and 0.55 g of 1-(3-aminopropyl)-4-(2-methoxyphenyl)-piperazine in 4 ml of anhydrous DMF. Immediately afterwards, 0.13 ml of triethylamine was added dropwise at the same temperature. After 30 minutes stirring at 0-5°C and 1 hour at room temperature, the reaction mixture was poured into 30 ml of water and extracted with ethyl acetate. The organic layer was washed with water, dried over anhydrous sodium sulphate and evaporated to dryness in vacuo. The crude product thereby obtained was dissolved in ethanol and 5N ethanolic hydrogen chloride was added. The title compound crystallized upon addition of diethyl ether.
Yield: 0.61 g. M.p. 210-213°C.

Example 26

2-Benzyl-N-{3-[4-(2-methoxyphenyl)-1-piperazinyl]-propyl}--benzamide dihydrochloride 0.125-H_2O

The title compound was prepared by the method described in Example 25 but using 2-benzylbenzoic acid instead of 2-phenylthio-benzoic acid. It was purified by crystallization from ethanol:diethyl ether and melted at 184-188°C.

Example 27

N-{3-[4-(2-Methoxyphenyl)-1-piperazinyl]-propyl}--2-phenethyl-benzamide dihydrochloride

The title compound was prepared by the method described in Example 25 but using 2-phenethyl-benzoic acid instead of 2-phenylthio-benzoic acid. It was purified by crystallization from ethanol:diethyl ether and melted at 186-189°C.

Example 28

N-{3-[4-(2-Methoxyphenyl)-1-piperazinyl]-propyl}--benzenesulphonamide

2 ml of benzenesulphonyl chloride was added dropwise at room temperature to a stirred solution of 3.74 g of 1-(3-aminopropyl)-4-(2-methoxyphenyl)-piperazine in 60 ml of ethanol-free chloroform. The mixture was stirred at room temperature for 2 hours, and then poured into 40 ml of 5.6N sodium hydroxide solution and extracted with chloroform. The organic layer was washed with water, dried over anhydrous sodium sulphate and evaporated to dryness in vacuo. The residue was purified by flash chromatography on silica gel eluting with a chloroform:5N methanolic ammonia 100:2 mixture, and crystallized from acetonitrile to give 3.5 g of

the title compound.
M.p. 125-127°C.

Example 29

N-{3-[4-(2-Methoxyphenyl)-1-piperazinyl]-propyl}-N-methyl--benzenesulphonamide dimethanesulphonate

The title compound was prepared by the method described in Example 28 but using 1-(2-methoxyphenyl)-4-(3-methylamino--propyl)-piperazine (prepared as described in WO 93/17007) instead of 1-(3-aminopropyl)-4-(2-methoxyphenyl)-piperazine. The crude base was dissolved in ethanol and 2 equivalents of a 2N ethanolic solution of methanesulphonic acid were added. The mixture was evaporated to dryness in vacuo. The residue was rinsed with ethyl acetate, stirred at reflux temperature for 1½ hours, filtered, and crystallized from acetonitrile to give the title compound. M.p. 166-167°C.

Example 30

2-[4-(2-Methoxyphenyl)-1-piperazinyl]-ethyl phenylacetate

The title compound was prepared according to the method described in Example 1 but using phenylacetic acid instead of benzoic acid and 1-(2-chloroethyl)-4-(2-methoxyphenyl)--piperazine instead of 1-(3-chloropropyl)--4-(2-methoxyphenyl)-piperazine. The reaction was conducted for 4 hours at 100°C. The crude product was purified by flash chromatography on silica gel, eluting with a dichloromethane:methanol 100:3 mixture. The crude was dissolved in diethyl ether, treated with charcoal, filtered, and evaporated to dryness to give the title compound as an oily residue.

NMR spectrum at 200 MHz, $CDCl_3$ (δ)
7.20-7.60 (m, 5H, CHs of phenyl ring)
6.80-7.18 (m, 4H, CHs of methoxyphenyl ring)

4.27	(t, 2H, $OC\underline{H}_2CH_2N$)
3.87	(s, 3H, OCH_3)
3.65	(s, 2H, CH_2COO)
2.95-3.15	(m, 4H, CH_2s in positions 3 and 5 of piperazine)
2.55-2.75	(m, 6H, CH_2s in positions 2 and 6 of piperazine and $OCH_2C\underline{H}_2N$)

Example 31

2-Benzyloxy-N-{3-[4-(2-hydroxyphenyl)-1-piperazinyl]-
-propyl}-benzamide hydrochloride

A mixture of 4.55 g of Intermediate XI, 2.1 g of anhydrous potassium carbonate and 2.7 g of 1-(2-hydroxyphenyl)-piperazine was stirred at 185-190°C for 30 minutes. After cooling to room temperature, 100 ml of chloroform and 60 ml of 1% aqueous sodium bicarbonate solution were added to the mixture and vigorously stirred. The organic layer was separated, washed with water, dried over anhydrous sodium sulphate, and evaporated to dryness in vacuo. The residue was purified by flash chromatography on silica gel eluting with a chloroform:5N methanolic ammonia 100:1 mixture. The so obtained base of the title compound was dissolved in methanol, acidified by addition of 1 equivalent of 5N ethanolic hydrogen chloride solution, and evaporated to dryness in vacuo to give a glassy solid. This was stirred with acetone, and then filtered off and crystallized from isopropanol to give 3.26 g of the title compound. M.p. 197-199°C.

Example 32

2-Methoxy-N-{3-[4-(2-methoxyphenyl)-1-piperazinyl]-propyl}-
-3-propionylbenzamide hydrochloride 1.1-H_2O

2.0 ml of diethyl cyanophosphonate and 1.67 ml of triethylamine were added at 0°C to a solution of 2.08 g of 2-methoxy-3-propionylbenzoic acid in 50 ml of anhydrous DMF.

2.99 g of 1-(3-aminopropyl)-4-(2-methoxyphenyl)-piperazine was then added. The reaction mixture was stirred at 0°C for 30 minutes and at room temperature for 2 hours, poured into water and extracted with ethyl acetate. The organic layer was dried on sodium sulphate and evaporated to dryness in vacuo. The residue was purified by flash chromatography, eluting with a dichloromethane:methanol 95:5 mixture, to give the base of the title compound. This was converted by the usual procedure into its hydrochloride which was crystallized from ethyl acetate yielding 2.4 g of the title compound. M.p. 133-134°C.

Example 33

3-Acetyl-2-benzyloxy-N-{3-[4-(2-methoxyphenyl)-
-1-piperazinyl]-propyl}-benzamide dihydrochloride

A solution of 4.35 g of Intermediate VI, 1.41 g of N-hydroxysuccinimide and 2.54 g of N,N'-dicyclohexyl-carbodiimide in 40 ml of anhydrous DMF was stirred for 2 hours at room temperature. After resting overnight, N,N'-dicyclohexylurea was filtered off by suction and 3.07 g of 1-(3-aminopropyl)-4-(2-methoxyphenyl)-piperazine was added to the filtrate. After 3 hours stirring at room temperature, the reaction mixture was poured into water and extracted with ethyl acetate. Following the usual work-up, the product was purified by flash chromatography (eluent ethyl acetate:methanol 95:5) yielding the base of the title compound. This was dissolved in dichloromethane and 2 molar equivalents of 0.92N ethanolic hydrogen chloride were added. Evaporation to dryness in vacuo and crystallization from acetonitrile gave 4.2 g of the title compound. M.p. 163-164°C.

Example 34

2-Benzyloxy-N-{3-[4-(2-methoxyphenyl)-1-piperazinyl]-
-propyl}-3-propionylbenzamide dihydrochloride

The title compound was obtained according to the procedure described in Example 33 but starting from 2.84 g of Intermediate II instead of Intermediate VI. 4.23 g were obtained, melting at 170-174°C (isopropanol).

Example 35

N-{3-[4-(2-Methoxyphenyl)-1-piperazinyl]-propyl}-2-
-(4-nitrobenzyloxy)-3-propionylbenzamide dihydrochloride hydrate

A solution of 1.43 g of Intermediate VII, 1.19 g of 1-(3-aminopropyl)-4-(2-methoxyphenyl)-piperazine, 0.8 g of diethyl cyanophosphonate and 0.67 ml of triethylamine in 21 ml of DMF was stirred at 0°C for 30 minutes and at room temperature for 2 hours, poured into water and extracted with ethyl acetate. After the usual work-up, the crude was purified by flash chromatography, eluting with ethyl acetate:methanol 95:5. This gave 2.15 g of the base of the title compound, which was converted into its hydrochloride and crystallized from acetonitrile. M.p. 164-170°C.

Example 36

N-{3-[4-(2-Methoxyphenyl)-1-piperazinyl]-propyl}-
-2-(4-nitrobenzyloxy)-benzamide

A mixture of 3.69 g of 3-[4-(2-methoxyphenyl)-
-1-piperazinyl]-propyl 2-hydroxybenzamide (prepared as described in EP 104614), 2.1 g of 4-nitrobenzyl chloride and 1.39 g of potassium carbonate in 50 ml of acetone was stirred at reflux for 3 hours. After cooling to room temperature, the reaction mixture was diluted with water.

The solid which precipitated was collected by suction and purified by flash chromatography, eluting with ethyl acetate:methanol (graduated from 100:2.5 to 100:5). The title compound thus obtained was recrystallized from ethanol, yielding 3.19 g, melting at 123-125°C.

Example 37

2-(4-Benzoylbenzyloxy)-N-{3-[4-(2-methoxyphenyl)-1-
-piperazinyl]-propyl}-3-propionylbenzamide dihydrochloride

The title compound was prepared according to Example 35 but starting from 3.03 g of Intermediate IX instead of Intermediate VII. Yield 3 g; m.p. 189-194°C (ethanol).

Example 38

2-(4-Benzoylbenzyloxy)-N-{3-[4-(2-methoxyphenyl)-
-1-piperazinyl]-propyl}-benzamide hydrochloride hydrate

The title compound was prepared according to the procedure of Example 36, but using 73% 4-benzoylbenzyl bromide (prepared as reported in Intermediate VIII) instead of 4-nitrobenzyl chloride and DMF as a solvent, stirring at room temperature. The crude was purified by flash chromatography eluting with an ethyl acetate:methanol mixture graduated from 85:5 to 90:20, yielding the base of the title compound. This was dissolved in isopropanol and converted to its hydrochloride by adding 5.8N isopropanolic hydrogen chloride. The solid was filtered and recrystallized from aqueous 0.1N hydrochloric acid. M.p. 165-169°C.

Example 39

N-{3-[4-(2-Methoxyphenyl)-1-piperazinyl]-propyl}-
-2-phenylethoxy-benzamide dihydrochloride

A mixture of 3.7 g of N-{3-[4-(2-methoxyphenyl)-

-1-piperazinyl]-propyl}-2-hydroxy-benzamide, 4.14 g of anhydrous potassium carbonate, 4.8 ml of phenethyl bromide, 0.05 g of potassium iodide and 30 ml of anhydrous DMF was stirred at room temperature for 8 hours. After cooling to room temperature, the mixture was evaporated to dryness in vacuo, diluted with water and extracted with chloroform. The organic layer was washed with water, dried over anhydrous sodium sulphate, and evaporated to dryness in vacuo. The residue was purified by flash chromatography on silica gel, eluting with chloroform:5N methanolic ammonia 100:1. The crude base was dissolved in ethanol and acidified with 5N ethanolic hydrogen chloride. Addition of diethyl ether gave a solid which was recrystallized from acetonitrile, yielding 1.12 g of the title compound, m.p. 165-166°C.

Example 40

2-Benzyloxy-N-{3-[4-(2-methoxyphenyl)-1-piperazinyl]--propyl}-phenylacetamide

The title compound was prepared according to the procedure described in Example 35 but starting from 2.08 g of 2-benzyloxy-phenylacetic acid (prepared as described in *J. Am. Chem. Soc.*, 64, 3051, 1942) instead of Intermediate VII. It was crystallized from diisopropyl ether. Yield 3.4 g; m.p. 98-104°C.

Example 41

2-Benzyloxy-N-{3-[4-(2-methoxyphenyl)-1-piperazinyl]--propyl}-N-methyl-benzamide dihydrochloride

0.64 ml of thionyl chloride was added to a solution of 1.82 g of 2-benzyloxybenzoic acid in 10 ml of dichloromethane and 0.064 ml of anhydrous DMF. After 1½ hours stirring at room temperature, the reaction mixture was cooled to 0°C and 2.4 g of 1-(2-methoxyphenyl)-4-(3-methylamino-propyl)-piperazine in 16 ml of dichloromethane was added. After 5 hours

stirring at room temperature, the reaction mixture was diluted with 4% sodium carbonate. The organic layer was separated off, dried on sodium sulphate and evaporated to dryness in vacuo. The crude was purified by flash chromatography (eluent chloroform:methanol 100:4) giving the base of the title compound. This was dissolved in isopropanol. 5.8N isopropanolic hydrogen chloride was added; the precipitated solid was collected by suction filtration and recrystallized from acetonitrile yielding 1.5 g of the title compound melting at 184-187°C.

Example 42

N-{3-[4-(2-Methoxyphenyl)-1-piperazinyl]-propyl}-
-2-(3-phenylpropoxy)-benzamide

The title compound was prepared by the method described in Example 39 but using 3-phenylpropyl bromide instead of phenethyl bromide. The crude product was purified by crystallization from isopropanol; m.p. 86-88°C.

Example 43

O-Ethyl-N-{3-[4-(2-methoxyphenyl)-1-piperazinyl]-propyl}-
-phenylphosphonamide

A solution of 2.04 g of O-ethyl phenylphosphonyl chloride (prepared as described in *Phosphorus and Sulphur*, 29, 169, 1987) in 70 ml of anhydrous diethyl ether was added dropwise at 5-15°C to a stirred solution of 4.98 g of 1-(3-aminopropyl)-4-(2-methoxyphenyl)-piperazine in 50 ml of anhydrous dichloromethane. After stirring at room temperature for 2½ hours, the precipitate was filtered and extracted with 70 ml of a 4:3 mixture of diethyl ether:dichloromethane, which then was evaporated to dryness in vacuo. The residue was purified by flash chromatography on silica gel eluting with dichloromethane: 5N methanolic ammonia (100:3) to give 3.67 g of the title compound as a

thick oil.

NMR spectrum at 200 MHz, $CDCl_3$ (δ)

7.70-7.90	(m, 2H, CHs in positions 2 and 6 of P-phenyl ring)
7.30-7.55	(m, 3H, CHs in positions 3, 4 and 5 of P-phenyl ring)
6.75-7.05	(m, 4H, CHs of methoxyphenyl ring)
3.90-4.25	(m, 3H, $OC\underline{H}_2CH_3$ and NH)
3.85	(s, 3H, OCH_3)
2.85-3.15	(m, 6H, CH_2s in positions 3 and 5 of piperazine and $PNHC\underline{H}_2CH_2CH_2$)
2.50-2.68	(m, 4H, CH_2s in positions 2 and 6 of piperazine)
2.47	(t, 2H, $PNHCH_2CH_2C\underline{H}_2$)
1.55-1.75	(m, 2H, $PNHCH_2C\underline{H}_2CH_2$)
1.33	(t, 3H, $OCH_2C\underline{H}_3$)

Example 44

N-{3-[4-(2-Methoxyphenyl)-1-piperazinyl]-propyl}-2-phenoxy--benzamide hydrochloride . 0.25 H_2O

The title compound was prepared by the method described in Example 25 but using 2-phenoxybenzoic acid instead of 2-phenylthiobenzoic acid. The title compound melted at 176-182°C after crystallization from a 1:4 mixture of ethanol:diethyl ether.

Example 45

N-{3-[4-(2-Methoxyphenyl)-1-piperazinyl]-propyl}-2-phenyl--benzamide 1.85-HCl 0.25-H_2O

The title compound was prepared by the method described in Example 25 but using 2-phenylbenzoic acid instead of 2-phenylthiobenzoic acid. The title compound melted at 192-195°C aft r crystallization from ethanol and resulted as a 1:0.425 mixture of monohydrochloride and dihydrochloride.

Elemental Analysis for $C_{27}H_{31}N_3O_2$ 1.85-HCl 0.25-H_2O
Calc.: C, 64.66; H, 6.70; N, 8.38; Cl, 13.01; H_2O, 0.90.
Found: C, 64.49; H, 6.63; N, 8.20; Cl, 12.81; H_2O, 0.74.

PHARMACOLOGICAL DATA

The receptor binding studies, as well as the experimental data on dogs reported below establish the compounds of the invention as α_1-blockers, i.e., to be within a class of substances widely used as agents that can be used fo the relief of symptoms associated with obstructive disorders of the lower urinary tract, including (but not limited to) benign prostatic hypertrophy (BPH), and as antihypertensives. See, e.g., W. H. Frishman et al., *Medical Clinics of N. America*, 72, 427, 1988 and references cited therein.

Methodology

Male Sprague Dawley rats [Crl: CD' BR] of 200-300 g b.w., female Albino Swiss mice [Crl: CD-1 (ICR) BR] 20-30 g b.w., and male Beagle dogs (10-12 kg b.w.) were obtained from Charles River, Italy and Nossan (Correzzana, Milan, Italy), respectively. Animals were housed with free access to food and water and maintained on forced light-dark cycle at 22-24°C until the day of experiments.

Acute toxicity

The acute toxicity of the compounds of the invention was evaluated in female Albino Swiss mice after intraperitoneal and oral administration. Four logarithmic scaled doses of the compounds were dissolved or suspended in 0.5% Methocel and each dose was administered in a volume of 10 ml/kg to groups of 4 mice. Mortality was recorded 7 days after the administration.

Data analysis : the LD_{50} values and their fiducial limits were calculated according to the method of Weil (*Biometrics*, 8, 249, 1952).

Receptor Binding Studies

The affinity of the compounds of the invention for the α_{1A}-adrenoceptor was investigated by utilizing [^{3}H]prazosin as radioligand and rat hippocampal membranes, after irreversible inactivation of α_{1B}-adrenoceptors with chloroethylclonidine, as source of the α_{1A}-adrenoceptors (C. Han et al., *Mol. Pharmacol.*, 32, 505, 1987).

Male rats were killed and their hippocampus was dissected, immediately frozen on dry ice and then stored at -70°C until use.

These tissues were homogenized (2 x 20 sec) in 50 vols of 50 mM Tris-HCl buffer, pH 7.4. The homogenates were centrifuged at 49000 x g for 10 min and the pellets were resuspended in 50 vols of the ice-cold buffer, incubated for 30 min at 37°C in the presence of 10 μM chloroethylclonidine (CEC) and recentrifuged at 49000 x g for 10 min. The pellets were washed once more in the ice-cold buffer without CEC. The final pellets were suspended in 80-120 vols of 50 mM Tris-HCl buffer, pH 7.4, containing 10 μM pargyline and 0.1% ascorbic acid.

The homogenates were incubated for 30 min at 25°C with 0.25-0.35 nM [^{3}H]prazosin in the absence or presence of the displacing compound to be tested, concentration ranging from 10^{-4} to $5x10^{-12}$ M, in a final volume of 2 ml. Non-specific binding was defined by 10 μM phentolamine.

The incubations were terminated by vacuum filtration over 0.2% polyethyleneimine pretreated Whatman GF/B fiber filters using Brandel cell harvester. The filters were then washed with 3x3 ml of ice-cold buffer and radioactivity retained on the filters was counted in 10 ml of Filter Count (Packard) in a liquid scintillation spectrometer with a counting efficacy of 40%. The ability of the tested compounds to displace the specific [^{3}H]prazosin binding was estimated

from the IC_{50} value, which is the molar concentration of unlabelled compound necessary to displace 50% of the specific binding. The IC_{50} values were estimated by the non-linear curve-fitting program Allfit (A. De Lean et al., *Am. J. Physiol.*, 235, E97, 1978).

Effects on Urethral Contractions and Blood Pressure in Dogs

The experiments were performed according to the method of Imagawa et al. (*J. Pharmacol. Methods*, 22, 103, 1989), with substantial modifications, as follows: adult male beagle dogs, weighing 8-10 Kg, were anaesthetized with pentobarbital sodium (30 mg/Kg i.v. and 2 mg/Kg/h i.v.), intubated for artificial breathing getting air from room. In order to monitor systemic blood pressure (BP), a PE catheter was introduced into the aortic arch through the right common carotid artery.

A collateral of the left femoral vein was cannulated for infusion of anaesthetic, and the right femoral vein was cannulated for administration of drugs. For intrarterial (i.a.) injection of noradrenaline (NA), a PE catheter was introduced into the lower portion of the abdominal aorta via the right external iliac artery. Through such a procedure, NA was selectively distributed to the lower urinary tract. Via a midline laparotomy, the urinary bladder and proximal urethra were exposed. In order to prevent the filling of the bladder, the two ureters were cannulated and the urine led outside. In order to record the prostatic urethral pressure, a Mikro-tip catheter (6 F) was introduced into the bladder via the external urethral meatus, and withdrawn until the pressure transducer was positioned in the prostatic urethra. A ligature was secured between the neck of the bladder and urethra to isolate the response of the latter and avoid any interaction with the bladder. Another ligature was put around the Mikro-tip catheter at the external urethral meatus, to secure the catheter itself. After a stabilizing period following surgical procedure (30 min), in which arterial and prostatic urethral pressure were continuously

monitored as basal values, i.a. administration of NA was made at intervals of 10 minutes. The dose of NA chosen was such to produce an increase of at least 100% in urethral pressure. The test compounds were administered i.v. in a cumulative manner with intervals of 15-20 min between administrations. I.a. injections of NA were repeated approximately 5 minutes after every dosing of test compound. Dose response curves were constructed computing the percentage inhibition to the increase in urethral pressure (NA induced), and the percentage drop in blood pressure produced by the test compound. ED_{25} for diastolic blood pressure (dose inducing a 25% decrease) and ID_{50} (dose inducing a 50% inhibition of NA-induced increase in urethral pressure) were computed by means of linear regression analysis.

Results

Compounds as prepared in the Examples were tested according to the methods reported above, and the results are given in the Tables below, together with comparative results for the reference standards used. Compounds having receptor affinity (IC_{50} values) lower than about 500 nM are generally considered to have good affinity. Compounds with IC_{50} values less than 100 nM are generally preferred.

TABLE I

Affinity for the α_{1A}-adrenoceptor and acute toxicity data

Compound Example No.	α_{1A}-Adrenoceptor Binding IC_{50} (nM)	Acute Toxicity in Mice LD_{50} (mg/kg) i.p.	p.o.
1	23	330	1624
2	14	351	1432
3	7	315	1915
4	8	250	1571
5	13	220	1426
6	8	59	539
7	135	80	383
8	33	>500	1206
9	47	381	
10	60	500	
11	13	>500	2000
12	8	>500	>2000
13	20	>500	>2000
14	11	>500	>2000
15	23.5	>500	>2000
16	12	>500	>2000
17	22	500	>2000
18		>500	
19		>500	>2000
20		>500	>2000
21		366	>2000
22		>500	>2000
23		>500	>2000
24		500	
25		71	
26		72	
27		74	
28		>500	513
29		60	183
31	5	85	
32	91		
Prazosin	1.4		1852
Urapidil	435	429	726

TABLE II

Effects on Urethral Contractility and Blood Pressure in Dogs

Compound Example No.	Urethra ED_{50} (μg/kg)	DBP ED_{25} (μg/kg)	DBP/Urethra ratio
3	52	349	6.7
6	23	377	16.4
Prazosin	3.6	6.6	1.8*
Urapidil	60.0	155.0	2.6*

Urethra: active dose in inhibiting by 50% the noradrenaline induced contraction of urethra

DBP: active dose in lowering diastolic blood pressure by 25%

DBP/urethra: ratio between the active doses (selectivity index)

*) non-selective: substantial effect on both urethra and DBP

Effective Amounts

The following represent guidelines to effective oral, parenteral or intravenous dose ranges expressed in mg/kg of body weight per day for the following uses:

In obstructive disorders of the lower urinary tract:

General	0.02 - 40
Preferred	0.1 - 2
Most Preferred	0.6 (oral dose)
Most preferred	0.006 - 0.06 (intravenous dose)

As antihypertensives:

General	0.02 - 40
Preferred	0.2 - 10
Most Preferred	2 (oral dose)
Most Preferred	0.02 - 0.2 (intravenous dose)

Selective use dosages, i.e. dosages that are active in the lower urinary tract without a substantial effect on the

blood pressure depend on the particular compound employed but, generally, up to four times the ED_{50} of a selective compound can be administered without substantial effect on blood pressure. Further refinements and optimization of dosages are possible using no more than routine experiments. The active compounds of the invention may be orally administered, for example, with an inert diluent or with an edible carrier, or they may be enclosed in gelatin capsules, or they may be compressed into tablets. For the purpose of oral therapeutic administration, the active compounds of the invention may be incorporated with excipients and used in the form of tablets, troches, capsules, elixirs, suspensions, syrups, wafers, chewing gum and the like. These preparations should contain at least 0.5% of active compounds, but the amount of active ingredient may be varied depending upon the particular form and may conveniently be from about 5% to about 70% of the weight of the unit. The amount of active compound in such compositions is such that a suitable dosage will be obtained although the desired dosage can be obtained by administering a plurality of dosage forms. Preferred compositions and preparations according to the invention are prepared so that an oral dosage unit form contains from 2 to 600 mg of active compound.

The tablets, pills, capsules, troches and the like may optionally contain any of the following ingredients: a binder such as micro-crystalline cellulose, gum tragacanth or gelatin; an excipient such as starch or lactose; a disintegrating agent such as alginic acid, Primogel, cornstarch and the like; a lubricant such as magnesium stearate or Sterotex; a glidant such as colloidal silicon dioxide; a sweetening agent such as sucrose or saccharin; or a flavouring agent such as peppermint, methyl salicylate, or orange flavouring. When the dosage unit form is a capsule, it may contain, in addition to materials of the above type, a liquid carrier such as a fatty oil. Other dosage unit forms may contain other various materials which modify the physical form of the dosage unit, for example, as coatings.

Thus, tablets or pills may be coated with sugar, shellac, or other enteric coating agents. A syrup may contain, in addition to the active compounds, sucrose as a sweetening agent and certain preservatives, dyes, colourings and flavours. Materials used in preparing these various compositions should be pharmaceutically acceptable and non-toxic in the amounts used.

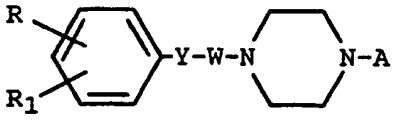
For the purpose of parenteral therapeutic administration, the active compounds of the invention may be incorporated into a solution or suspension. These preparations should contain at least 0.2% of active compound, but may be varied between 0.5 and about 30% of the weight thereof. The amount of active compound in such compositions is such that a suitable dosage will be obtained. Preferred compositions and preparations according to the present invention are prepared so that a parenteral dosage unit contains from 0.4 to 200 mg of active compound.

The solutions or suspensions may also include the following components: a sterile diluent such as water for injection, saline solution, fixed oils, polyethylene glycols, glycerine, propylene glycol or other synthetic solvents; antibacterial agents such as benzyl alcohol or methyl parabens; antioxidants such as ascorbic acid or sodium bisulphite; chelating agents such as ethylenediaminetetraacetic acid; buffers such as acetates; citrates or phosphates and agents for the adjustment of tonicity such as sodium chloride or dextrose. The parenteral multiple dose vials may be of glass or plastics material.

Additional compositions suitable for administration by various routes and containing compounds according to the invention are also within the scope of the invention. Dosage forms, additional ingredients and routes of administration contemplated herein include those disclosed in US 4089969 and 5091182.

CLAIMS

1. A compound of the general formula I:

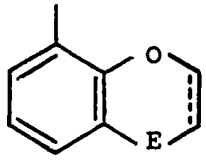


wherein

Y represents a valence bond or one of the following groups, each of which is depicted with its left hand end being the end which attaches to the phenyl group and its right hand end being the end which attaches to the group W:
$-S(O)n-$, $-N(R_2)-$, $-N(R_2)CO-$, $-PO(OC_2H_5)NH-$, $-NHCONH-$, $-CO-$, $-SO_2N(R_2)-$, $-(CH_2)_nCOO-$ and $-(CH_2)_nCON(R_2)-$,
wherein
n is 0 to 2, and
R_2 represents a hydrogen atom, an alkyl group having up to 4 carbon atoms, a carbamoyl group, or an alkanoyl or alkylcarbamoyl group each having from 2 to 5 carbon atoms;

W represents a linear or branched alkylene group having from 2 to 6 carbon atoms;

A represents (i) a substituted phenyl group, the or each substituent being a halogen atom or an alkoxy, alkyl or hydroxy group, the substituent or one of the substituents being in the 2-position, or (ii) a group of the formula



wherein
---- represents a single or double bond, and
E represents an oxygen atom or a valence bond;

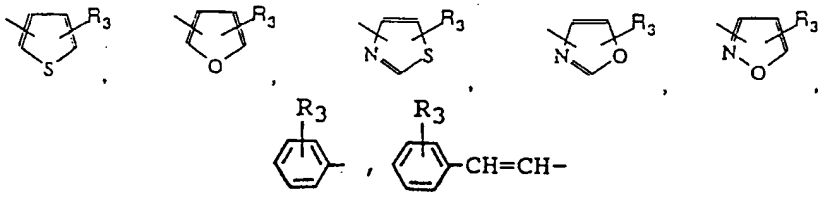
R represents a group of the formula $-X-(CH_2)_p-Z$,

wherein

X represents a valence bond or one of the following groups, each of which is depicted with its left hand end being the end which attaches to the phenyl group and its right hand end being the end which attaches to the group $-(CH_2)_p-Z$:
$-O-$, $-S(O)_n-$, $-CO-$, $-N(R_2)-$, $-N(R_2)CO-$ and $-N(R_2)SO_2-$;
wherein n and R_2 are as above defined;

p is 0 to 10, and

Z represents a hydrogen atom, a cycloalkyl group having from 4 to 8 carbon atoms, a 1-naphthyl group, a 2-naphthyl group, a diphenylmethyl group or one of the groups having the following formulae



wherein R_3 has the same values as R_1 defined below; and

R_1 represents one or more hydrogen or halogen atoms or cyano, hydroxy, alkoxy, alkyl, trifluoromethyl, alkanoyl, α-hydroxyalkyl, nitro, amino, alkylamino, dialkylamino, alkanoylamino, alkylsulphonylamino, phenyl, phenoxy or benzoyl groups;

with the provisos that:

when Y represents a valence bond or one of the groups $-S(O)_n-$, $-N(R_2)-$, $-CH_2CON(R_2)-$ or $-CH_2CH_2CON(R_2)-$, Z does not represent a hydrogen atom unless p is greater than 3;

when Y represents one of the groups $-N(R_2)CO-$, $-CO-$ or $-CON(R_2)-$, the group R is in the ortho position relative to the moiety Y and either (i) the group R_1, not being a hydrogen atom, is in the ortho position

relative to the group R or (ii) Z does not represent a hydrogen atom unless p is greater than 3 and

when Y represents a sulphur atom and R represents the group $C_6H_5CH=CHCONH$, R_1 does not represent a hydrogen atom.

or a prodrug, enantiomer, diastereoisomer, crystalline form, solvate, N-oxide or pharmaceutically acceptable salt of such a compound.

2. A compound according to claim 1 in which Y represents a group -COO- or -CONH-, depicted as stated in claim 1.

3. A compound according to claim 1 or claim 2 in which W represents a trimethylene group.

4. A compound according to any preceding claim in which A represents a 2-methoxyphenyl group.

5. Any one of the following compounds:
3-[4-(2-methoxyphenyl)-1-piperazinyl]-propyl benzoate,
3-[4-(2-methoxyphenyl)-1-piperazinyl]-propyl 2-methoxybenzoate,
3-[4-(2-methoxyphenyl)-1-piperazinyl]-propyl 2-benzyloxy--benzoate,
3-[4-(2-methoxyphenyl)-1-piperazinyl]-propyl 2-methoxy--3-propionylbenzoate,
3-[4-(2-methoxyphenyl)-1-piperazinyl]-propyl 2-benzyloxy--3-propionylbenzoate,
2-benzyloxy-N-{3-[4-(2-methoxyphenyl)-1-piperazinyl]--propyl}-benzamide,
2-hydroxy-N-{3-[4-(2-methoxyphenyl)-1-piperazinyl]-propyl}--3-propionylbenzamide,
3-[4-(2-methoxyphenyl)-1-piperazinyl]-propyl 2-hydroxybenzoate,
3-[4-(2-methoxyphenyl)-1-piperazinyl]-propyl 3-benzyloxy--benzoate,
3-[4-(2-methoxyphenyl)-1-piperazinyl]-propyl 4-benzyloxy-

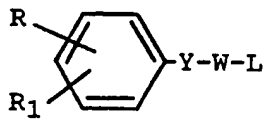
-benzoate,
3-[4-(2-methoxyphenyl)-1-piperazinyl]-propyl
2-(2-chlorobenzyloxy)-benzoate,
3-[4-(2-methoxyphenyl)-1-piperazinyl]-propyl
2-(3-chlorobenzyloxy)-benzoate,
3-[4-(2-methoxyphenyl)-1-piperazinyl]-propyl
2-(4-chlorobenzyloxy)-benzoate,
3-[4-(2-methoxyphenyl)-1-piperazinyl]-propyl
2-(2-methoxybenzyloxy)-benzoate,
3-[4-(2-methoxyphenyl)-1-piperazinyl]-propyl
2-(3-methoxybenzyloxy)-benzoate,
3-[4-(2-methoxyphenyl)-1-piperazinyl]-propyl
2-(4-methoxybenzyloxy)-benzoate,
3-[4-(2-methoxyphenyl)-1-piperazinyl]-propyl
2-(2,3-dimethoxybenzyloxy)-benzoate,
3-[4-(2-methoxyphenyl)-1-piperazinyl]-propyl
2-(3,4-dimethoxybenzyloxy)-benzoate,
3-[4-(2-methoxyphenyl)-1-piperazinyl]-propyl
2-(3,4,5-trimethoxybenzyloxy)-benzoate,
3-[4-(2-methoxyphenyl)-1-piperazinyl]-propyl
2-octyloxybenzoate,
3-[4-(2-methoxyphenyl)-1-piperazinyl]-propyl
2-butoxybenzoate,
3-[4-(2-methoxyphenyl)-1-piperazinyl]-propyl
2-cyclohexylmethoxybenzoate,
3-[4-(2-methoxyphenyl)-1-piperazinyl]-propyl
2-(2-naphthylmethoxy)-benzoate,
2,2-dimethyl-3-[4-(2-methoxyphenyl)-1-piperazinyl]-propyl
2-benzyloxybenzoate,
N-{3-[4-(2-methoxyphenyl)-1-piperazinyl]-propyl}-
-2-phenylthio-benzamide,
2-benzyl-N-{3-[4-(2-methoxyphenyl)-1-piperazinyl]-propyl}-
-benzamide,
N-{3-[4-(2-methoxyphenyl)-1-piperazinyl]-propyl}-
-2-phenethyl-benzamide,
N-{3-[4-(2-methoxyphenyl)-1-piperazinyl]-propyl}-
-benzenesulphonamide,
N-{3-[4-(2-methoxyphenyl)-1-piperazinyl]-propyl}-N-methyl-

-benzenesulphonamide,
2-[4-(2-methoxyphenyl)-1-piperazinyl]-ethyl phenylacetate,
2-benzyloxy-N-{3-[4-(2-hydroxyphenyl)-1-piperazinyl]-
-propyl}-benzamide,
2-methoxy-N-{3-[4-(2-methoxyphenyl)-1-piperazinyl]-propyl}-
-3-propionylbenzamide,
3-acetyl-2-benzyloxy-N-{3-[4-(2-methoxyphenyl)-
-1-piperazinyl]-propyl}-benzamide,
2-benzyloxy-N-{3-[4-(2-methoxyphenyl)-1-piperazinyl]-
-propyl}-3-propionylbenzamide,
N-{3-[4-(2-methoxyphenyl)-1-piperazinyl]-propyl}-
-2-(4-nitrobenzyloxy)-3-propionylbenzamide,
N-{3-[4-(2-methoxyphenyl)-1-piperazinyl]-propyl}-
-2-(4-nitrobenzyloxy)-benzamide,
2-(4-benzoylbenzyloxy)-N-{3-[4-(2-methoxyphenyl)-1-piperazin
yl]- -propyl}-3-propionylbenzamide,
2-(4-benzoylbenzyloxy)-N-{3-[4-(2-methoxyphenyl)-
-1-piperazinyl]-propyl}-benzamide,
N-{3-[4-(2-methoxyphenyl)-1-piperazinyl]-propyl}-2-phenyleth
oxy- -benzamide,
2-benzyloxy-N-{3-[4-(2-methoxyphenyl)-1-piperazinyl]-
-propyl}-phenylacetamide,
2-benzyloxy-N-{3-[4-(2-methoxyphenyl)-1-piperazinyl]-
-propyl}-N-methyl-benzamide,
N-{3-[4-(2-methoxyphenyl)-1-piperazinyl]-propyl}-
-2-(3-phenylpropoxy)-benzamide,
O-ethyl-N-{3-[4-(2-methoxyphenyl)-1-piperazinyl]-propyl}-
-phenylphosphonamide,
N-{3-[4-(2-methoxyphenyl)-1-piperazinyl]-propyl}-2-phenoxy-
-benzamide, and
N-{3-[4-(2-methoxyphenyl)-1-piperazinyl]-propyl}-2-phenyl-
-benzamide;
or a pharmaceutically acceptable salt thereof.

6. A pharmaceutical composition comprising a compound according to any preceding claim, or a prodrug, enantiomer, diastereoisomer, crystalline form, solvate, N-oxide or pharmaceutically acceptable salt of such a compound, in

admixture with a pharmaceutically acceptable diluent or carrier.

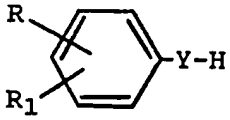
7. A method for the preparation of a compound according to claim 1, the method comprising condensing a compound of the general formula II



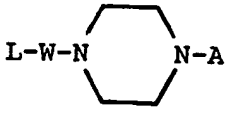
wherein R, R_1, Y and W are as defined in claim 1 and L represents a halogen atom or a leaving group with a piperazine derivative of the general formula III

wherein A is as defined in claim 1.

8. A method for the preparation of a compound according to claim 1, the method comprising condensing a compound of the general formula IV

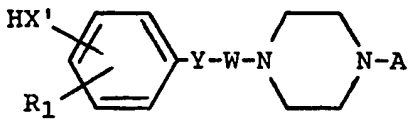


wherein R, R_1, and Y are as defined in claim 1 with a piperazine derivative of the general formula V



wherein W and A are as defined in claim 1 and L represents a halogen atom or a leaving group.

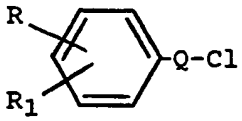
9. A method for the preparation of a compound of the general formula I in which Y, W, A and R_1 are as defined in claim 1 and R represents a group of the general formula $X'-(CH_2)_p-Z$ wherein X' represents an oxygen or sulphur atom or an imino or alkylimimo group, the method comprising condensing a compound of the general formula VI



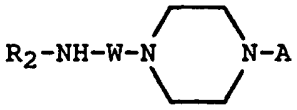
with a compound of the general formula $Z-(CH_2)_p-L$ wherein L represents a halogen atom or a leaving group.

10. A method according to any of claims 7 to 9, which method is carried out in the optional presence of a base (such as potassium carbonate) either at from 20 to 140°C in a polar solvent (such as dimethylformamide of methanol) or at from 100 to 200°C in the absence of solvent.

11. A method for the preparation of a compound of the general formula I in which W, A, R and R_1 are as defined in claim 1 and Y represents a group of the formula $-(CH_2)_nCON(R_2)-$, $-SO_2N(R_2)-$ or $-PO(OC_2H_5)NH-$, R_2 and n being as defined in claim 1, the method comprising condensing a compound of the general formula VII



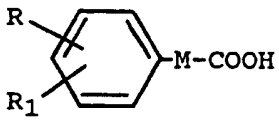
wherein R and R_1 are as defined in claim 1 and Q represents a group of the formula $-(CH_2)_nCO-$, $-SO_2-$ or $-PO(OC_2H_5)-$, with a compound of the general formula VIII



wherein W, A and R_2 are as defined in claim 1.

12. A method according to claim 11, which method is carried out either in an aprotic solvent (such as a haloalkane, toluene, dimethylformamide or pyridine) in the optional presence of an organic base (such as triethylamine) or in aqueous dioxane or a lower alkanol in the presence of an inorganic base (such as sodium hydroxide, sodium bicarbonate or potassium carbonate).

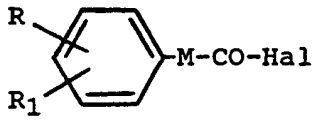
13. A method for the preparation of a compound of the general formula I in which W, A, R and R_1 are as defined in claim 1 and Y represents a group of the formula $-(CH_2)_nCONH-$, n being 0 to 2, the method comprising condensing a compound of the general formula IX



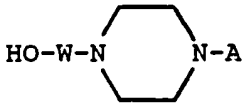
wherein R and R_1 are as defined in claim 1 and M represents a group $-(CH_2)_n-$ wherein n is 0 to 2 with a compound of the general formula VIII as defined in claim 11.

14. A method according to claim 13, which method is carried out in the presence of a coupling agent (such as dicyclohexylcarbodiimide, N,N'-carbonyldiimidazole or diethyl cyanophosphonate) and an optional promoting agent (such as 4-dimethylaminopyridine, N-hydroxybenzotriazole or N-hydroxysuccinimide) in an aprotic or chlorinated solvent at from -10 to 140°C.

15. A method for the preparation of a compound of the general formula I in which W, A, R and R_1 are as defined in claim 1 and Y represents a group of the formula $-(CH_2)_nCOO-$ wherein n is 0 to 2, the method comprising condensing a compound of the general formula X



wherein R and R_1 are as defined in claim 1, M represents a group $-(CH_2)_n-$ wherein n is 0 to 2 and Hal represents a halogen atom with a compound of the general formula XI



wherein W and A are as defined in claim 1.

INTERNATIONAL SEARCH REPORT

Internat l Application No
PCT/EP 94/02437

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D295/08 C07D295/12 A61K31/495 C07F9/6509

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D C07F

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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A	US,A,3 846 430 (JACQUES DE ANTONI ET. AL.) 5 November 1974 *Document* ---	1-15

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
4 November 1994	11. 11. 94

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax (+31-70) 340-3016	Luyten, H

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A	US,A,4 857 644 (MAGID A. ABOU-GHARBIA) 15 August 1989 *Complete document; particularly example 5*	1-15

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